HTA44

Convergent but Not Equivalent: National HTA Evidentiary Flexibility and Residual Evidence Adaptation Under Joint Clinical Assessment

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Introduction

- The implementation of European Union (EU) Regulation 2021/2282 established Joint Clinical Assessment (JCA) to provide a shared scientific assessment of clinical evidence, reduce duplication, and support national health technology assessment (HTA) processes across Member States.[1,2]
- Although clinical evidence is assessed jointly, national HTA bodies remain responsible for interpreting the evidence within the local healthcare context to inform national appraisal, pricing, and reimbursement decisions.[1,2]
- The practical effectiveness of JCA may depend not only on whether national HTA bodies converge in their methodological expectations, but also on whether they converge around permissive, conditional, or restrictive evidentiary positions, with different implications for country-specific evidence adaptation.
- This study assessed cross-country convergence and evidentiary flexibility of current HTA methodologies to identify where JCA may reduce duplication and where country-specific evidence adaptation may persist.

Methods

- A cross-sectional comparative review of publicly available national HTA methodological guidance was conducted across 11 EU Member States: Belgium, Denmark, France, Germany, Ireland, Italy, the Netherlands, Poland, Portugal, Spain and Sweden. Countries were selected to provide geographic and economic diversity and represent established HTA systems.
- Guidance was reviewed across nine clinical evidence domains, spanning established requirements and emerging evidence areas; two reviewers independently coded each country-domain methodological position using an ordered, descriptive framework:
  - *A: most flexible or manufacturer-accommodating*
  - *B: conditionally flexible*
  - *C: most restrictive or conservative*
  - *D: guidance absent, unclear, or insufficiently specified*
- The coding was based on explicit requirements or preferences in official guidance rather than inferred HTA practice; coding discrepancies were resolved through discussion and consensus between the two reviewers.
- Cross-country convergence was calculated for each domain as the proportion of assessed countries sharing the modal methodological category:
  - *Convergence score = Countries in the modal category ÷ Countries assessed*
- Convergence was classified as high (≥75%), moderate (50% to 74%), or low (<50%). Supplementary concentration and dispersion analyses using the Herfindahl–Hirschman Index and normalised Shannon entropy were conducted to assess the robustness of the modal-category findings.
- An HTA Flexibility Index (FI) was developed to quantify evidentiary flexibility. Categories A, B, and C were assigned scores of 1.00, 0.50, and 0.00, respectively with Category D excluded. Mean FI scores were calculated at both domain and country level, and classified as high (≥0.67), moderate (≥0.34 to <0.67) or low (<0.34).

Results

- A total of 99 country-domain combinations were coded across 11 countries and nine clinical evidence domains. An overview of study coverage and the relationship between convergence and flexibility is presented in **Figure 1** and **Figure 2**, respectively.
- Three domains demonstrated high convergence, although the direction of alignment differed:
  - Comparator requirements converged entirely on the most restrictive category (C=100%), reflecting consistent expectations for locally relevant standard-of-care comparators rather than manufacturer-selected or non-local comparators.
  - Endpoint expectations and uncertainty management converged on conditional flexibility (B=100% and B=91%, respectively), indicating that surrogate endpoints and residual uncertainty were generally acceptable only when supported by validation evidence, justification, or mitigation strategies.
- RWE and external control arms showed moderate convergence on conditional flexibility (B=64% for both), reflecting acceptance of RWE as supportive evidence and conditional acceptance of external controls with methodological caveats.
- ITCs showed moderate convergence, with countries divided between broad and conditional acceptance (A=45%/B=55%), but were the most flexible domain overall (mean flexibility score=0.73).
- Subgroup analyses showed the greatest variation, with low convergence (45%) and an equal distribution of conditionally flexible and restrictive positions (B=45%/C=45%). Requirements ranged from clinical justification of pre-specified analyses to statistically robust, pre-specified subgroup effects.
- Published guidance was frequently absent or unclear for emerging evidence areas: Category D was assigned for biomarker-defined subgroups in six countries (55%) and extrapolation of immature evidence in five countries (45%).
- Country-level HTA Flexibility Index scores ranged from 0.17 (low) in Germany to 0.56 (moderate) in the Netherlands. Eight countries demonstrated moderate flexibility, while France, Germany, and Portugal were categorised as having low flexibility (**Figure 1**).

Country	Comparator requirements	Endpoint expectations	RWE acceptance	External control arms	Indirect treatment comparisons	Subgroup analyses	Biomarker-defined subgroups	Uncertainty management	Extrapolation of immature evidence	HTA FI (Country)
France	C	B	B	B	B	C	C	B	B	0.33
Germany	C	B	C	C	B	C	C	B	C	0.17
Italy	C	B	B	D	B	D	D	B	D	0.40
Spain	C	B	B	B	A	C	D	B	D	0.43
Netherlands	C	B	A	B	B	B	B	A	B	0.56
Sweden	C	B	B	B	B	B	D	B	D	0.43
Poland	C	B	B	B	A	B	B	B	C	0.44
Portugal	C	B	C	C	A	C	D	B	D	0.29
Belgium	C	B	C	D	B	B	B	B	D	0.36
Denmark	C	B	B	B	A	B	D	B	B	0.50
Ireland	C	B	B	B	A	C	D	B	B	0.44
HTA FI (Domain)	0.00	0.50	0.41	0.39	0.73	0.25	0.30	0.55	0.55	

A Most flexible · B Conditionally flexible · C Most restrictive · D Guidance absent / unclear

Figure 1. National HTA evidentiary flexibility across countries and clinical evidence domains

Cells show coded methodological positions (A, most flexible; B, conditionally flexible; C, most restrictive; D, guidance absent or unclear). Mean HTA Flexibility Index (HTA FI) scores are shown by country (right) and domain (bottom); Category D was excluded from index calculations

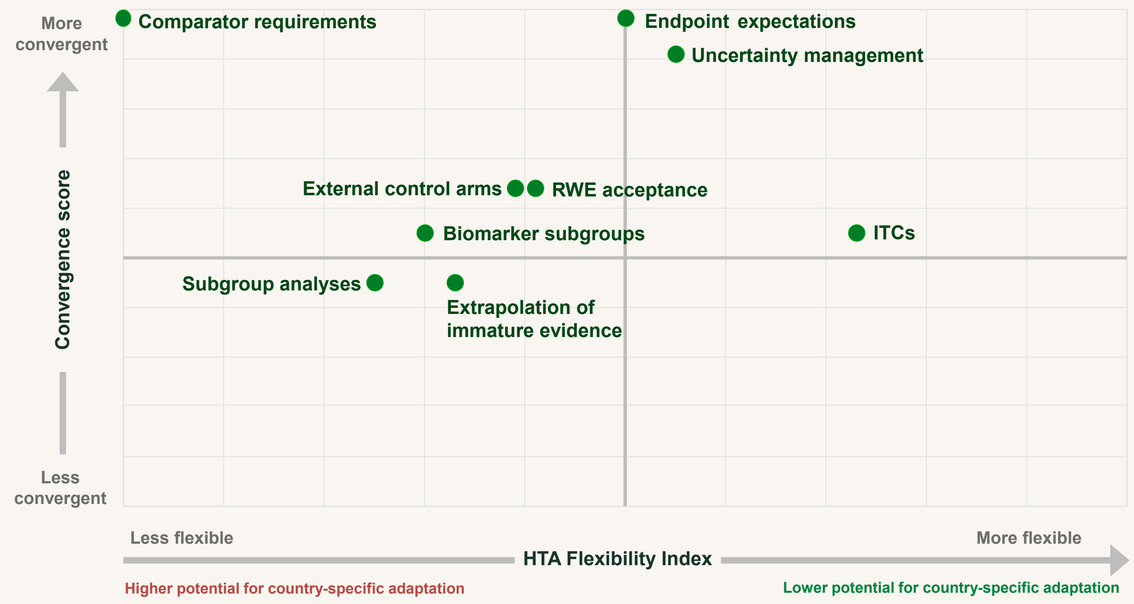


Figure 2 . Relationship between cross-country convergence and evidentiary flexibility across clinical evidence domains

Each point represents a domain; convergence reflects modal-category agreement across countries, and the HTA Flexibility Index indicates the direction of requirements from restrictive to flexible. Points further left indicate more restrictive methodological requirements and may therefore be associated with higher potential for country-specific evidence adaptation. Points further right indicate greater methodological flexibility and may be associated with lower adaptation potential. However, adaptation may also depend on cross-country convergence. This relationship is exploratory

Conclusions

- Cross-country convergence in national HTA requirements does not necessarily indicate equivalent evidentiary positions, as alignment may occur around either flexible or restrictive expectations.
- JCA may reduce duplication where national requirements are concentrated, but variation in evidentiary tolerance is likely to maintain country-specific adaptation needs, particularly for uncertainty, subgroup evidence and non-traditional evidence designs.
- Under-specification of biomarker-defined subgroups and extrapolation of immature evidence highlights methods-guidance gaps in areas central to precision and high-uncertainty therapies, potentially creating uncertainty or inconsistency in national interpretation of JCA findings for oncology medicines and advanced therapy medicinal products (ATMPs).
- Manufacturers developing high-uncertainty or precision therapies should anticipate national evidence requirements alongside the common EU evidence package, while future research should assess whether convergence in published guidance translates into greater consistency in HTA appraisals and reimbursement decisions.

References

1. European Parliament and Council of the European Union. Regulation (EU) 2021/2282 of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. Official Journal of the European Union. 2021;L458:1-32.
2. European Commission. Joint Clinical Assessments. Available at: https://health.ec.europa.eu/health-technology-assessment/implementation-regulation-health-technology-assessment/joint-clinical-assessments_en. Accessed June 2026.

Abbreviations

ATMPs, advanced therapy medicinal products; EU, European Union; FI, flexibility index; HHI, Herfindahl–Hirschman index; HTA, health technology assessment; ITC, indirect treatment comparison; JCA, Joint Clinical Assessment; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RWE, real-world evidence.

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